

CASE REPORT

Narcolepsy after A/H1N1 vaccination

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INTRODUCTION

Narcolepsy is defined as a pentad of symptoms that include excessive daytime sleepiness, disturbed nocturnal sleep, sleep paralysis, cataplexy, and hypnagogic or hypnopompic hallucinations (1). The cause of narcolepsy is still unknown, although it has been associated with a combination of genetic and environmental factors; the prevalence is approximately 0.04% (2). The peak age of onset is the second decade of life, and onset after age 55 or prior to age 10 is rare. Not every symptom is present in all patients, and the severity is also variable (2).

Hypocretin, a neuropeptide of hypothalamic origin, has been involved in the pathogenesis of narcolepsy. The CSF hypocretin-1 levels are very low or even undetectable in most narcoleptic patients with cataplexy. The HLA-DQB1*0602 allele, which is involved in the control of the hypocretin receptor, is also present in 88% to 98% of such patients (2).

The association between narcolepsy and vaccination against the 2009 pandemic influenza A (H1N1) virus was initially suggested in 2010 in Finland and Sweden, leading to the suspension of vaccination in these countries (3). Additional cases were subsequently reported (4-5).

Herein, we describe a patient with narcolepsy with cataplexy syndrome after A/H1N1 vaccination in Brazil and discuss the potential causes and treatment.

CASE REPORT

A 19-year-old woman, first observed in May 2010, 40 days after being vaccinated against the 2009 pandemic influenza A (H1N1) virus (PandemrixTM - Lot A80CA254A), complained of acute and intense headache. Physical examination and general blood tests were unremarkable. A few days later, she presented with uncontrollable sleep attacks, a sensation of "dreaming with open eyes", nightmares, and a poor quality of sleep. An electroencephalogram, an MRI of the skull, and thyroid laboratory test results were all found to be normal. She gained 9 kg (19.8 lbs) in two months. In September, she presented with cataplexy, hypophonia, and weakness in all

limbs without falls. In February 2011, she experienced an episode of sleep paralysis but no hypnagogic hallucinations. The results of a neurological examination were normal.

The patient scored 19 points on the Epworth Somnolence Scale. Polysomnography disclosed a sleep efficiency of 81.8% and a sleep latency of three minutes. She did not display apnea/hypopnea but had a Respiratory Effort Related Arousal (RERA) index of 72, which was normalized with nasal Continuous Positive Airway Pressure (CPAP) (8 cm H₂O). She subsequently presented with very stable sleep. The multiple sleep latency test, performed one week after the introduction of nasal CPAP to avoid false-positive results, revealed sleep latencies between 1 and 6.5 minutes, and three sleep onset rapid eye movement periods (SOREMPs) lasting from 8 to 12 minutes. Notably, the patient carries the HLA-DQB1* 06:02 allele. The CSF hypocretin level could not be determined because the test was not available in the state of Minas Gerais.

Based on the overall clinical findings and on the results from the ancillary tests, a diagnosis of narcolepsy was made (6). Appropriate communication to the public service for pharmacological vigilance and to the company responsible for the production of the vaccine were first undertaken on September 30, 2010. The patient was treated with modafinil (200 mg/day) for hypersomnolence and venlafaxine (37.5 mg/day) for cataplexy. This approach to treatment achieved an excellent clinical response.

DISCUSSION

There is some evidence that narcolepsy is an autoimmune disorder or involves an infectious agent with participation of the immune system (7-8). Cases of narcolepsy after 2009 pandemic influenza A (H1N1) virus vaccination have been described in Sweden, Finland, Canada, France, and the United States (3). The diagnosis was defined by the association of hypersomnolence, cataplexy, presence of the HLA DQB1*0602 allele, a positive multiple sleep latency test for narcolepsy, and low CSF hypocretin levels. By January 2011, 162 patients vaccinated with PandemrixTM presenting narcolepsy were reported to GlaxoSmithKline (5).

Reported cases experienced an onset of symptoms ranging from two days to five months (usually two to eight weeks) after vaccination, intense and unusual hypersomnolence, cataplexy, rapid weight gain, and atypical age for narcolepsy. Most cases received vaccines with ASO3 as an adjuvant (PandemrixTM and ArepanrixTM), which are associated with stronger immune responses, and not with PanenzaTM. An association

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between narcolepsy, streptococcal infection and A/H1N1 influenza has also been reported (3). Putative mechanisms include trigger of a specific immune response to A/H1N1 followed by molecular mimicry or generalized stimulation of the immune system (3). The WHO Independent Global Advisory Committee on Vaccine Safety reported no increased risk of narcolepsy associated with the use of any vaccine in the past (5).

The presented case occurred after A/H1N1 vaccination with ASO3. The clinical and neurophysiologic features, plus the HLA genotype, even without CSF hypocretin data, fulfill the diagnosis of narcolepsy, according to the recently published Brazilian guidelines (6). Such guidelines state that the determination of CSF hypocretin levels is mandatory only in cases of narcolepsy without cataplexy or in patients with negative multiple sleep latency test results. Considering the temporal association between the vaccination and the emergence of the clinical symptoms, there may be a link with the vaccine. Interestingly, however, our patient presented with cataplexy (hypocretin receptor-2 knockout) without fragmented sleep patterns (no hypocretin receptor-1 knockout), suggesting a link between receptor-2 and susceptibility to this vaccine.

Post-vaccine narcolepsy may be less rare than previously thought. Diagnosis in the early stages would allow for the

use of certain treatment options such as immunosuppressors that may be able to arrest or at least delay hypocretin cell loss (8), and/or the use of the usual stimulant and antidepressant drugs.

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